



## Overview of Materials for Chloroprene PBPK Peer Review

- Focus of this peer review and possible next steps
- U.S. EPA Background for Peer Review
- U.S. EPA Charge Questions
- Ramboll PBPK report and supplements (appendices)
- Ramboll model code packages (zip files)
  - Ramboll 2020 Chloroprene In Vitro Code.zip
  - Ramboll 2020 Chloroprene PBPK Code.zip
- Public comments are available at:

<https://www.regulations.gov/docket?D=EPA-HQ-ORD-2020-0181>





## Focus of Peer Review

- ◆ Focus of current peer review: Is the chloroprene PBPK model sufficiently reliable for use in an IRIS Toxicological Review?
  - Prediction of chloroprene tissue concentrations in mice, rats, and humans
  - Prediction of chloroprene oxidative metabolism in lung, liver, and kidney of mice, rats, and humans
- ◆ But this peer review is not to address **how** the PBPK model will be applied.
- ◆ While lung may be the highest risk tissue, review should not focus only on it.
- ◆ If the model is found sufficiently reliable, then “how” it is applied would be addressed in a subsequent EPA analysis, which would undergo external review.
- ◆ Detailed presentation of charge questions will be covered in Versar presentation.



## Items in Package

- **U.S. EPA Background for Peer Review**

- Provides context for model evaluation
- Request for Correction / Request for Reconsideration of IRIS Tox Review:  
<https://www.epa.gov/quality/epa-information-quality-guidelines-requests-correction-and-requests-reconsideration#l7002>
- If a PBPK model is accepted, EPA usually tries to apply it comprehensively

- **U.S. EPA Charge Questions**

- Grouped by model component and element of analysis
- In Vitro Model → PBPK Model → Uncertainty Analysis
- Includes pointers to specific text and results being addressed



## Items for Review #2

- **Ramboll (2020) report**
  - Primary document gives overview of modeling analysis
  - Technical details in Supplement documents
- **Ramboll model packages (.zip files)**
  - Ramboll 2020 Chloroprene In Vitro Code.zip
  - Ramboll 2020 Chloroprene PBPK Code.zip
- **EPA reviewed, provided comments & suggestions to Ramboll on previous versions**
  - Incorporates two-compartment in vitro model, per EPA's suggestion
  - EPA did not review final version
  - Ramboll authors will be present to answer questions during peer review meeting



## Items for Review #3

- **U.S. EPA Uncertainty Analysis (UA)**

1. Alternate UA of in vitro parameter uncertainty
  - Partly complete due to COVID-19 (access to computer)
  - Evaluation of statistical model & approach requested
  - Results would be reviewed again in next phase
2. Approach to quantify uncertainty of PBPK model
  - Requires completion of UA #1 as input (and other data)
  - Evaluation of method requested
  - Major flaws, missing elements?
  - Specific details and results would be reviewed again in next phase